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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/551,977 | 04/14/2000 | John M. Polo | 930049.489/1593.004 | 2230 |

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| EXAMINER | |
|---|---|
| LI, BAO Q | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1648 | |

DATE MAILED: 06/03/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/551,977 | POLO ET AL. | |
| | Examiner | Art Unit | |
| | Bao Qun Li | 1648 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *22 April 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *17 and 19-23* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *17,19 and 21-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

### RCE

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 04/22/2004 has been entered. The RCE follows:

### *Response to Amendment*

This is a response to the amendment, paper No. 34, filed 04/22/04. Claim 7 has been amended. Claims 7 and 19-23 are pending and considered before the examiner.

Please note any ground of rejection(s) that has not been repeated is removed. Text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

**New Grounds of Rejections:**

### *Claim Rejections - 35 USC § 112*

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 17, 19 and 21-23 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for having a recombinant Sindbis virus, which has a substantive mutation at amino acid residue 160 from Gly to Glu of said Sindbis virus E2 protein and is able to infect the human dendritic cell (DC), does not reasonably provide enablement for having any or all recombinant alphavirus comprising an alphavirus replicon that comprises a mutation at the position at amino acid position selected from 158-162 of E2, wherein the virus particle is able to infect human DC . The specification does not enable any person skilled in the

art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

3. The test of scope of the enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the application coupled with information known in the art would undue experimentation (See United States v. Theketronic Inc., 8USPQ2d 1217 (fed Cir. 1988). Whether undue experimentation is required is not based upon a single factor but rather a conclusion reached by weighting many factors. Theses factors were outlined in Ex parte Forman, 230 USPQ 546 (Bd. Pat. App. & Inter. 1986) and in re Wands, 8USPQ2d 1400 (Fed. Cir. 1988). These factors include the following:

4. 1). Unpredictability of the art. The initial target cells for the alphavirus infection is not clear and whether any or all recombinant alphaviruses can infect human DC is unpredictable. Some point mutation may accidentally be able to abolish the infective ability of an alphavirus for human DC. For example, McDonald et al. (J. Virol. 2000, Vol. 74, pp. 914-922) reported that a recombinant alphavirus Venezuelan Equine Encephalitis vector carrying a green fluorescence protein can infect DC, however, a substitution mutation from Glu to Lys at the residue 76 totally abolish the ability for the said virus to infect DC, whereas an mutation of Lys to Glu at the residue 116 of E2 restore the ability for infecting DC (see entire document).

5. 2) State of the art. The initial target cell for the alphavirus infection is poorly understood. The art at has demonstrated that mutation at the E2 region of alphavirus can alter the virus neurovirulence and viral entry into the cells as evidenced by Tucker et al. (J. Virol. 1997, Vol. 71, pp. 6106-6112, see entire document) and McDonald et al. described supra (J. Virol. 2000, Vol. 74, pp. 914-922, see entire document). Polo's group, an inventor of instant application, (Gardner et al. J. Virol. Dec. 2000, Vol. 74, pp. 11849-11857) reports that a Sindbit virus with a substitution mutation of Gly to Glu at the residue 160 of E2 region can infect human dendritic cell. However, they concluded that the level of the toxicity of the mutated Sindbits virus to the primary human DC unfortunately prevent them to do further investigation (see entire document).

6. 3) Number of working examples. Applicants present no working examples of any other alphavirus except a recombinant Sindbit virus with a substitution mutation of Gly to Glu at the residue 160 of E2 region that can infect human DC.

7. 4) Amount of guidance presented in the specification. Proteins are made from 20 amino acids. Along the range of amino acid residues 158-162, there are 5 positions can be mutated among many alphaviruses. Applicants present no guidance on how the skilled artisan would practice successfully with any or all recombinant alphavirus vector having a mutation at such a position that is able to let the mutant be able to infect human DC.

8. 5) Scope of the claims. The claims broadly read on any or all recombinant alphavirus having a mutation at any position selected from 158 to 162 of E2 protein, which is able to infect human DC.

9. 6) Nature of the invention. The invention involves a complex and unpredictable field.

10. 7) Lever of the skill in the art. The requirement of level of the skill for constructing a recombinant alphavirus vector with an ability to infect human DC is high. Without proper guidance, a large quantity of non-routine experiment has to be conduct for constructing and selecting a recombinant alphavirus being ca[able to infect the human DC.

11. Given the above analysis of the factors, which the courts have determined, are critical in asserting whether a claimed invention is enabled, it must be considered that the skilled artisan would have had to conduct undue and excessive experimentation in order to practice the claimed invention.

12. Claims 21-23 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

13. In the instant case, the specification only teach that they has isolated a mutated Sindbis virus being able to infect human dentritic cells, which has a substantive mutation at amino acid residue 160 from Gly to Glu of said Sindbis virus E2 protein. However, Applicants do not have a possession for having any other isolated alphavirus clone having a mutation at the position selected from amino acid residue 158-162 of E2 protein that is able to infect human DC.

14. Applicants' attention is directed to the case law of *University of California v. Eli Lilly and Co.*, 43 USPQ2d 1398 (Fed. Cir. 1997), which teaches that the disclosure of a process for

obtaining cDNA from a particular organism and the description of the encoded protein fail to provide an adequate written description of the actual cDNA from that organism which would encode the protein from that organism, despite the disclosure of a cDNA encoding that protein from another organism. In this content, 35 USC 112 requires inter alia that "a patent specification contains a written description of the invention and the manner and process of making and using it in such full clear and concise terms as to enable one skilled in the art to make and use the invention". Case law has also made it clear that the requirements for a "written description" and an "enabling disclosure" are separate. For example, where a specification contains sufficient information to enable a skilled chemist to produce a particular compound because it gives detailed information on how to produce analogous compounds but it makes no reference to the compound in question, the "written description" requirement has not been met even though the description may be enabling. In the instant case, while the method of substitutive mutation at position of 158-162 can be made according to the technique known in the art, but it make no reference to an isolated alphavirus mutant in question. Therefore, the claims are rejected.

**********

15. Claim 20 is deemed free of prior art, given failure of the prior art to teach or reasonably suggest that a recombinant Sindbits virus with substitution mutation from Gly to Glu at the residue 160 of E2 region car able to infect human DC. The closest art taught by Klimstra et al (J. Virol. 1998, Vol. 72, pp. 7357-7366) or Tunker et al. (J. Virol. 1997, Vol. 71, pp. 6106-6112) teach that some substitutive mutation of a single amino acid located at the different position of E2 region, which can increase the binding ability of the Sindbits virus to baby hamster kidney cells (BHK) or change the virulence. However, there is no indication that any mutation at the E2 region can enable Sindbits virus infect human DC.

***Conclusion***

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bao Qun Li whose telephone number is 703-305-1695. The examiner can normally be reached on 7:00 to 4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on 703-308-4027. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Bao Qun Li
Art Unit 1648
May 18, 2004

James C. Housel 6/1/04

JAMES HOUSEL
SUPERVISORY PATENT EXAMINER
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